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Evidence for Genetic Factors Explaining the Birth Weight–Blood Pressure Relation

Analysis in Twins

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Abstract—Epidemiological studies have consistently shown an inverse association between birth weight and systolic blood pressure in later life after adjustment for current size. To examine whether this association is explained by intrauterine or genetic factors, we investigated birth weight and blood pressure data in 53 dizygotic and 61 monozygotic adolescent twin pairs. Birth weight was obtained from the mothers. Blood pressure measurements were performed 6 times at rest and during mental stress. The dizygotic but not the monozygotic twins with the lowest birth weight from each pair had a systolic blood pressure measured at rest and during the reaction time experiment that was higher compared with their cotwins with the highest birth weight (dizygotic twins: blood pressure at rest, 119.4±9.7 mm Hg versus 117.3±8.5 mm Hg, $P=0.07$, and during a reaction time task, 126.2±10.8 versus 123.6±9.5, $P=0.09$; monozygotic twins: blood pressure at rest, 117.4±6.4 versus 118.4±9.0, $P=0.4$, and during a reaction time task, 122.9±8.4 versus 124.2±10.8, $P=0.2$). The differences in blood pressure between the cotwins with the lowest and the cotwins with the highest birth weight were different in dizygotic compared with monozygotic twin pairs (for blood pressure at rest, $P=0.05$; for blood pressure during reaction time, $P=0.03$). After adjustment for differences in current weight, intrapair differences in birth weight were negatively and significantly associated with differences in systolic blood pressure at rest and during the reaction time task in dizygotic twins (regression coefficient, −5.7 mm Hg/kg [95% confidence interval, −10.4 to −1.0] and −6.3 [−12.7 to 0], respectively) but not in monozygotic twins (−0.1 [−5.4 to 5.2] and +3.5 [−1.8 to 8.8], respectively). Interaction analysis indicated that the associations were different between dizygotic twins and monozygotic twins ($P=0.1$ and $P<0.05$, respectively). These data suggest that genetic factors may play an important role in the association between birth weight and blood pressure. **(*Hypertension*. 2000;36:1008-1012.)**

Key Words: blood pressure ■ genetics ■ twins

Epidemiological studies have consistently shown an inverse association between birth weight and systolic blood pressure (SBP) from childhood to adulthood.[1–5] One leading theory postulates that intrauterine programming in response to fetal malnutrition induces permanent changes in the structure and function of organs that cause raised blood pressure.[6] However, human exposure to famine in utero did not result in a significantly higher blood pressure.[7,8] Alternatively, it has been proposed that genetic factors influencing both birth weight and blood pressure could explain the relations between these two factors.[9] In other words, the genotype responsible for raised blood pressure may itself cause retarded fetal growth in utero.

Twin studies offer a unique opportunity to distinguish between intrauterine and genetic influences.[10] Specifically, differences within dizygotic twin pairs are a function of both genetic and nongenetic factors, whereas differences within monozygotic (identical) pairs are almost completely caused by nongenetic factors.[10] If genetic factors do not play a role in the association between birth weight and blood pressure, it could be expected that both for dizygotic and for monozygotic twins, the twin with the lowest birth weight from each pair will also have the highest blood pressure compared with the co-twin with the highest birth weight. In addition, negative associations between intrapair differences in birth weight and intrapair differences in blood pressure should exist both in dizygotic and in monozygotic twins. If, however, genetic factors do play a role, these associations would hold true only for dizygotic twins, not for monozygotic twins. In two previous twin studies, it has been suggested that the association between birth weight and blood pressure is independent from genetic factors.[11,12] However, these studies[11,12] could not specifically examine differences between dizygotic and monozygotic twins because the results of the

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intrapair analyses of the differences in birth weight with differences in blood pressure in both dizygotic and monozygotic twins were not statistically significant in either study. To reexamine this issue, we analyzed birth weight and blood pressure data in a large group of adolescent twin pairs still living with their parents. Blood pressure was measured at rest and during mental stress, which is an important early predictor for the development of essential hypertension.[13,14]

Methods

Subjects

This study is part of a larger project in which cardiovascular risk factors were studied in 160 adolescent twin pairs and their parents.[15–17] Addresses of twins living in Amsterdam and neighboring cities were obtained from city council population registries. Twins still living with their biological parents were contacted by letter. From the families initially willing to participate, several had to be excluded because not all four family members could find the time to participate or could speak Dutch sufficiently. After including sufficient monozygotic twins, only dizygotic twins were included to create approximately equal groups of monozygotic and dizygotic twins. Overall, between 30% and 40% of the families complied.[15] Zygosity was determined as described in detail previously.[15] A questionnaire was used to gather information on various factors including the use of medication and smoking behavior. The maternal questionnaire included questions regarding birth weight and gestational age of their children. This questionnaire was sent to the mothers a few weeks ahead of their visit to our department, allowing them to obtain birth data from birth certificates. Opposite-sex dizygotic twin pairs were excluded because of the effects of gender differences within a pair on both birth weight and blood pressure. Subjects taking oral contraceptives were excluded for these analyses. None of the subjects used any other medication that may affect blood pressure. Thus, 53 dizygotic and 61 monozygotic twin pairs were eligible for analysis.

Measurements

Height and weight were measured in a standardized way. After acclimatization, blood pressure was measured 6 times at rest and during reaction time (RT) and mental arithmetic (MA) tasks as described in detail previously.[15] During RT, subjects had to press a "yes" button when a high tone and a "no" button when a low tone was heard over the earphones. During MA, subjects had to add up 3 numbers that were presented in succession on a television screen. After 5 seconds, an answer to the addition problem appeared on the screen. Subjects were asked to press the "yes" button when a correct answer and the "no" button when a wrong answer appeared on a screen. The means of the 6 measurements at rest and during both stress tasks were calculated. All blood pressure measurements were performed with an oscillometric technique (Dinamap 845XT, Critikon Inc).

Statistical Methods

In the total group, linear regression analysis was used to investigate the influence of birth weight on blood pressure after adjustment for gender and after additional adjustment for current weight.[1–5] Associations of current weight with birth weight and blood pressure were investigated with correlation analysis after adjustment for gender. An interaction analysis was performed to investigate whether zygosity, current weight, or current body mass index (BMI) influenced the associations between birth weight and blood pressure by introducing a product term of these variables and birth weight into the regression model. The paired *t* test was used to compare twins with the lowest birth weight from each pair with their cotwins with the highest birth weight. For this analysis, 2 dizygotic and 2 monozygotic twin pairs had to be excluded because the birth weight of the twins within a pair was equal. The differences in dizygotic twin pairs and in monozygotic twin pairs were compared by means of the independent samples *t* test. Linear regression analysis was used to analyze whether intrapair differences in birth weight influenced intrapair differences in blood pressure before and after adjustment for differences in current weight in dizygotic and monozygotic twins (including the 4 twin pairs in which the birth weight of the twins within a pair was equal). To create a wide range in intrapair differences with both positive and negative values, intrapair differences in birth weight were calculated by randomly subtracting the co-twin with the lowest birth weight from the co-twin with the highest birth weight or vice versa. After ensuring that the regression lines passed through the origin in both dizygotic and monozygotic twins (ie, the intercept was not significantly different from 0), interaction analysis was performed to investigate whether zygosity influenced the associations between intrapair differences in birth weight and differences in blood pressure, A 2-tailed probability value of <0.05 was considered significant. All analyses were performed on a personal computer with the statistical software package SPSS version 7.5 (SPSS Inc).

TABLE 1. Association Between Birth Weight and Blood Pressure in Twins

Variable	β (95% Confidence Interval, mm Hg/kg	*P*
Adjusted for gender		
SBP		
At rest	−0.5 (−2.6 to 1.5)	0.6
During RT	−2.1 (−4.5 to 0.3)	0.09
During MA	−2.8 (−5.6 to 0)	0.05
Adjusted for gender and current weight		
SBP		
At rest	−1.9 (−3.9 to 0.0)	0.05
During RT	−3.6 (−6.0 to −1.2)	<0.01
During MA	−4.6 (−7.4 to −1.8)	<0.01

Results

In the total group of twins, negative associations between birth weight and blood pressure were found after adjustment for gender, although the association with blood pressure at rest and during RT was not significant (Table 1). After adjustment for gender, current weight was associated with birth weight ($r=0.26$, $P<0.001$) and blood pressure measured at rest, during RT, and during MA ($r=0.32$, $r=0.23$, and $r=0.23$, respectively, $P<0.001$) more strongly than was BMI (data not shown). After additional adjustment for current weight, the negative associations of birth weight with SBP were strengthened (Table 1). Interaction analysis indicated that these associations were not significantly modified by zygosity, current weight, or current BMI (data not shown).

Comparison Between Cotwins With Lowest and Cotwins With Highest Birth Weight

Birth weight and gestational age were similar in dizygotic and monozygotic twins (Table 2). The differences in birth weight between the cotwins with the lowest birth weight and those with the highest birth weight from each pair were similar for dizygotic and monozygotic twin pairs (380 g and 300 g, respectively; *P* for the difference, 0.2; Table 2). Both dizygotic and monozygotic twins with the lowest birth weight from each pair were lighter than their cotwins with the highest birth weight, whereas BMI was similar. The dizygotic twins

TABLE 2. Clinical Characteristics of Cotwins with Lowest and Highest Birth Weight in Dizygotic and Monozygotic Twin Pairs

	Dizygotic Twin Pairs			Monozygotic Twin Pairs		
Variable	Cotwins With Lowest Birth Weight	Cotwins With Highest Birth Weight	*P*	Cotwins With Lowest Birth Weight	Cotwins With Highest Birth Weight	*P*
Birth weight, g	2246±493	2626±558	<0.001	2336±528	2636±485	<0.001
Gestational age, wk	36±8.4	36±8.4	...	37±2.8	37±2.8	...
n (male/female)	59 (32/27)	59 (32/27)	...	51 (30/21)	51 (30/21)	...
Age, y	17.0±1.7	17.0±1.7	...	16.0±1.8	16.0±1.8	...
BMI, kg/m^2	20.0±1.9	20.3±2.2	0.5	19.5±2.2	19.7±2.2	0.2
Current weight, kg	59.9±7.8	61.8±10.1	0.09	57.7±9.6	58.9±9.3	0.03
Smoking, n	7	9	...	4	4	...
SBP, mm Hg						
At rest	119.4±9.7	117.3±8.5	0.07	117.4±6.4	118.2±9.0	0.4
During RT	126.2±10.8	123.6±9.5	0.09	122.9±8.4	124.2±10.8	0.2
During MA	129.2±12.6	128.1±12.6	0.6	128.1±9.2	128.2±10.9	0.9

Values are mean±SD.

with the lowest birth weight had an SBP measured at rest and during RT that was higher than that of their cotwins with the highest birth weight. However, the monozygotic twins with the lowest birth weight had an SBP that was similar to that of their cotwins with the highest birth weight (Table 2). The differences in blood pressure between the cotwins with the lowest and the cotwins with the highest birth weight were different in dizygotic compared with monozygotic twin pairs (for blood pressure at rest, $P=0.05$; for blood pressure during RT, $P=0.03$).

Associations Between Intrapair Differences

To further characterize the relation between birth weight and blood pressure, we determined the associations between intrapair differences in birth weight and differences in blood pressure. Table 3 shows that intrapair differences in birth weight were negatively associated with differences in SBP at rest and during RT in dizygotic twins but not in monozygotic twins. After adjustment for differences in current weight, intrapair differences in birth weight were significantly and negatively associated with differences in blood pressure at rest and during RT (Table 3). For example, a positive difference in birth weight of 1 kg within pairs was associated with a negative difference in SBP at rest of 5.7 mm Hg in dizygotic twin pairs and a negative difference of 0.1 mm Hg in monozygotic twin pairs. Interaction analysis indicated that the associations were significantly different between dizygotic twins and monozygotic twins for SBP during RT ($P<0.05$), and the associations tended to be significantly different for SBP at rest ($P=0.1$).

If subjects with a gestational age <37 weeks (21 dizygotic and 24 monozygotic twin pairs) were excluded, the results were similar. Adjustment for gestational age or (differences in) smoking did not change the results. For diastolic blood pressure, comparable results were obtained as for SBP, but the differences between dizygotic and monozygotic twins were not significant (data not shown).

TABLE 3. Associations Between Intrapair Differences in Birth Weight and Differences in SBP in Dizygotic and Monozygotic Twin Pairs

	Dizygotic Twin Pairs		Monozygotic Twin Pairs	
Variable	β (95% Confidence Interval, mm Hg/kg)	*P*	β (95% Confidence Interval, mm Hg/kg)	*P*
Unadjusted				
SBP, mm Hg				
At rest	−3.7 (−8.1 to 0.8)	0.10	+0.4 (−4.7 to 5.6)	0.9
During RT	−5.2 (−11.0 to 0.7)	0.08	+3.7 (−1.4 to 8.8)	0.2
During MA	−0.6 (−8.3 to 7.0)	0.9	+1.6 (−4.2 to 7.3)	0.6
Adjusted for differences in current weight				
SBP, mm Hg				
At rest	−5.7 (−10.4 to −1.0)	0.02	−0.1 (−5.4 to 5.2)	0.9
During RT	−6.3 (−12.7 to 0)	0.05	+3.5 (−1.8 to 8.8)	0.2
During MA	−2.6 (−11.0 to 5.7)	0.5	+1.0 (−4.9 to 7.0)	0.7

Discussion

In accordance with previous studies in singletons,[1–5] we found negative associations between birth weight and blood pressure after adjustment for current weight in twins. In dizygotic twin pairs, the twins with the lowest birth weight from each pair tended to have a higher blood pressure compared with their cotwins with the highest birth weight. In addition, significant negative associations between intrapair differences in birth weight and intrapair differences in SBP measured at rest and during RT were observed after adjustment for differences in current weight. To eliminate the influence of genetic factors on these associations, we also studied monozygotic twin pairs. Despite a similar difference in birth weight as in dizygotic twins, the monozygotic twins with the lowest birth weight had blood pressures similar to those of their cotwins with the highest birth weight. In addition, in the monozygotic twins, there was no negative association between intrapair differences in birth weight and differences in SBP. When dizygotic and monozygotic twins were compared, the differences in blood pressure between the twins with the lowest birth weight and their cotwins with the highest birth weight were significantly different for blood pressure measured at rest and during RT. These data provide the first evidence that genetic factors influence the association between the variance in birth weight and that in blood pressure.

Because the intrapair analyses could not exclude a negative association between birth weight and blood pressure in monozygotic twins, the possibility that intrauterine factors also influence the relation between birth weight and blood pressure cannot be ruled out. However, the comparison of dizygotic twins with monozygotic twins demonstrates that elimination of genetic factors abolishes the strong association between birth weight and blood pressure. Therefore, our results suggest that genetic factors may play an important role in the birth weight–blood pressure relation but cannot exclude additional intrauterine influences.

Our results seem contradictory to the conclusions from two previous twin studies.[11,12] However, these studies[11,12] could not specifically examine differences between dizygotic and monozygotic twins because the results of the intrapair analyses of the differences in birth weight with differences in blood pressure in both dizygotic and monozygotic twins were not statistically significant in either study. In the study of Dwyer et al,[11] only 16 monozygotic twins were included, and the results of Poulter et al[12] are also open to another interpretation. Poulter et al compared intrapair differences in blood pressure in 4 strata of intrapair differences in birth weight (0, 1 to 500 g, 501 to 1000 g, and >1000 g) and concluded that the relation between birth weight and blood pressure is probably independent of genetic factors. However, a closer look at their data shows that the opposite may be true. As a first intrapair analysis, blood pressure levels between cotwins with the highest and the lowest birth weight from each pair should be compared in all dizygotic and monozygotic twins, which can be calculated from the data presented in their report. After adjustment for confounding factors, the 203 dizygotic but not the 140 monozygotic twins with the highest birth weight had an SBP that was significantly lower compared with their cotwins with the lowest birth weight (difference in blood pressure, −5.37 mm Hg, $P<0.05$, and −0.85 mm Hg, $P=0.8$, respectively). This suggests that the relation between birth weight and blood pressure within twin pairs differs between dizygotic and monozygotic twins, which is in accordance with our results.

Approximately two thirds of monozygotic twins are monochorionic (ie, share a placenta), whereas all dizygotic twins are dichorionic (ie, have separate placentas). Therefore, it could be argued that besides genetic factors, intrauterine factors may also differ between dizygotic and monozygotic twins and may be the cause of the difference in the intrapair association between birth weight and blood pressure. We do not have data on chorionicity in our group of monozygotic twins, but a recent study in monozygotic twins demonstrated that in both monochorionic and dichorionic monozygotic twins, the twins with the lowest birth weight from each pair had a blood pressure that was lower than their cotwins with the highest birth weight.[18] Although focused on another subject and based on a relatively small number of twins, these data demonstrate that differences in the intrauterine environment between dizygotic and monozygotic twins are not a likely explanation for the differences in the intrapair associations between birth weight and blood pressure.

In animal studies, it has been demonstrated that maternal undernutrition during pregnancy retards fetal growth and elevates blood pressure.[19] However, this may reflect the selective survival of fetuses genetically susceptible to hypertension, with a possible role for insulin resistance.[20] Interestingly, in human studies of maternal undernutrition,[7,8] birth weight in the offspring was lowered but blood pressure in later life was not elevated, which is consistent with an important role for genetic factors.

The size of the association between intrapair differences in birth weight and differences in blood pressure in dizygotic twins is larger than the size of the association between birth weight and blood pressure observed in previous studies of singletons.[1–5] This is probably due to the elimination of various confounding characteristics, such as gestational age, maternal factors (eg, height, weight gain, smoking, and blood pressure during pregnancy), social class, birth order (in relation to other siblings), ethnic origin, and gender.

To our knowledge, this is the first study to examine the association between birth weight and blood pressure measured during mental stress. It has been demonstrated that an enhanced cardiovascular response to stress is an early predictor for the development of essential hypertension.[13,14] We found that the association of birth weight with blood pressure during both stress tasks was higher than with blood pressure measured at rest. This emphasizes the increased risk of the development of future hypertension in subjects born with a low birth weight and suggests that the mechanism responsible for the enhanced response to stress plays a role in the association between low birth weight and hypertension. The associations between intrapair differences in birth weight and differences in blood pressure were in the same direction for blood pressure at rest, during RT and during MA. However, the differences between dizygotic and monozygotic twins were less clear cut for blood pressure measured during MA than at rest and during RT. Although it has been demonstrated

that heritability of blood pressure increases during both MA and RT compared with blood pressure at rest,[15,21] our findings suggest that genetic factors are less important in the association of birth weight with blood pressure during MA than with blood pressure at rest and during RT.

In our group of twins, the negative associations between birth weight and blood pressure were strengthened after adjustment for current weight, which showed a stronger association with both birth weight and blood pressure than did BMI. Furthermore, the negative associations between intrapair differences in birth weight and differences in blood pressure in dizygotic twin pairs were strengthened after the adjustment for differences in current weight. This is in accordance with previous studies that show that adjustment for current size (ie, weight in young subjects and BMI in adults) increases the strength of the association of birth weight with blood pressure.[3,4,22–24] Adjusting for current size has often been justified on the grounds that birth weight is positively related to later size and that current weight is positively related to blood pressure, and, if not adjusted for, could obscure a negative relation between birth weight and blood pressure.[25] However, Lucas et al[25] suggested that this interpretation is incorrect and proposed that it is the change in size from birth to later life rather than size at birth itself that is implicated. In our study, the associations were strengthened after adjustment for current size. This suggests that both size at birth and change in size from birth to later life are associated with higher blood pressure in later life.

In our study, no significant interaction of either current BMI or weight on the relation between birth weight and blood pressure could be observed, suggesting that the strength of the association between birth weight and blood pressure was not larger in subjects with a high than in subjects with a low current BMI or weight. This is consistent with the results from some studies[26,27] but is in contrast to the findings of others.[5,23,24]

It has been suggested that improvement of fetal nutrition and thereby intrauterine growth may prevent the development of cardiovascular disease.[6] However, if the relation between low birth weight and raised blood pressure is caused by genetic factors, improvement of fetal nutrition may not prevent the development of raised blood pressure. Low birth weight may only serve as a marker of increased risk of raised blood pressure.

In summary, we found a tendency toward higher blood pressure levels in the twins with the lowest birth weight from each pair compared with their cotwins with the highest birth weight and negative associations between intrapair differences in birth weight and differences in blood pressure in dizygotic twins but not in monozygotic twins. This difference in the birth weight–blood pressure relation between dizygotic and monozygotic twin pairs suggests that genetic factors may play an important role in the association between birth weight and blood pressure.

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